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Clozapine vs. Haloperidol in Aggression Prevention

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Abstract

Nurses and physicians working in forensic psychiatric facilities are frequently exposed to violent incidents at the hands of forensic psychiatric patients and inmates. Aside from seclusion, segregation and restraint, prevention serves as an efficient strategy in dealing with violence and aggression, including a proper medication regimen. This paper aims to address a specific clinical research question in terms of prevention of violence and aggression among forensic psychiatric patients, from a pharmaceutical perspective. **Clinical Question**: In forensic psychiatric patients with a history of aggression, is regular use of Clozapine more effective in reducing the incidence of violence and/or aggression than regular use of Haloperidol? Five primary research studies were found to be specific to the clinical question and its context. **Review results**: Resulting from its superior efficacy in treating complicated, positive schizophrenia symptoms, including violence and aggression, Clozapine may be better situated to prevent aggressive incidents among Forensic Patients with a history of aggression. Answering the clinical question has led to reflection and application of new recommendations of pharmaceutical interventions in a forensic setting.

Keywords: Violence, aggression, forensic psychiatry, Haloperidol, Clozaril

Introduction

Forensic psychiatric patients have a long history of violence and aggression towards staff, themselves and other residents. Nurses and physicians working in forensic psychiatric facilities are therefore frequently exposed to violent incidents at the hands of residents. There are many instigators to violence in this population, such as acute psychosis, disinhibition, personality disorders and being in an environment where violence and aggression is considered a cultural “norm” (Kelly et al., 2015).

Many strategies and safety measures have been employed in attempts to mitigate violence and aggression in the forensic setting. Likely due to the proliferation of new research, a paradigm shift in forensic psychiatry is emerging in which the use of locked seclusion, segregation and mechanical restraints are being discouraged while alternative solutions to aggression mitigation are being advocated. Presently, the most effective measure against the use of seclusion, segregation and restraint is that of prevention. Prevention has come in the form of risk assessments, a proper medication regimen and counseling (Fluttert et al, 2008). These strategies are conducive to healing and maintain therapeutic rapport with patients, through risk assessments, 1 on 1 patient counseling and the use of PRN (pro re nata or as needed) medications in addition to regular medication regimens, in order to deal with feelings of anxiety, frustration and impulsivity (Fluttert et al., 2008; Kelly et al., 2015). However, other strategies still commonly employed to handle aggressive behaviour are more harmful, such as the use of locked seclusion and segregation, the use of mechanical restrains and the use of chemical restraints (Stoner et al., 2002).

Despite this growing body of research about violence prevention, there is still much to learn about effective prevention strategies against violence and aggression, especially in forensic psychiatric patients.

While this paper briefly outlines some of the emerging data, research and strategies being employed in the prevention of violence and aggression among forensic psychiatric patients, a full analysis and review of these strategies is beyond its scope. Instead, this paper aims to address a specific clinical research question about the prevention of violence and aggression through the administration of psychotropic drugs, among forensic psychiatric patients. In forensic psychiatric patients with a history of aggression, is regular use of Clozapine more effective in reducing the incidence of violence and/or aggression than regular use of Haloperidol?

Clinical Question

The population of forensic psychiatric patients may be considered a relatively broad term, as it represents a specific demographic segment, with multifactorial characteristics that predispose them to violence and aggression. These may include diagnoses of major psychiatric illness such as schizophrenia, or otherwise personality disorders such as antisocial personality, a history of violent behaviour and living in an environment in which violence and aggression are cultural “norms”.

The clinical question refers to an intervention in administering Haloperidol (Haldol) or Clozapine (Clozaril) targeting the specific outcome of reducing / eliminating aggression and violence. The comparison will uncover

witch of the two medications produces a more significant effect in the prevention of aggression and violence.

These specific interventions become the focus of the clinical question as it relates to the extensive use of the two medications in forensic psychiatry. Violence/aggression is viewed here in terms of violent acts, aggressive outbursts (yelling, shouting, and threatening) and includes staff injuries associated with patient behaviour.

Clinical Reasoning

Any clinical question being proposed needs to have a sound, clinical rationale. While many therapies and interventions in medicine and nursing have been found to be effective without a well understood causality, it is still important, when posing any clinical question, to ensure that the question is processed based on clinical evidence and knowledge. In fact, Hoffmann, Bennett and Del Mar (2013) argue that knowledge is a fundamental requirement for the effective implementation of evidence-based practice.

Haloperidol and Clozapine are both atypical antipsychotics, predominantly used in treating schizophrenia (Citrome & Volavka, 2013). Clozapine has generally been reserved for severe and refractory cases of schizophrenia, especially in patients who exhibit aggression (Chengappa et al., 2002). Studies comparing Clozapine to Haloperidol have found that patients receiving Clozapine experience generally less side effects, including less incidences of tardive dyskinesia and extrapyramidal side effects, which might explain why patients receiving Clozapine show better adherence to therapy (Kane et al., 2001; Kurz et al., 1995), less hospital stays, and less withdrawal symptoms. However, Clozapine has been found to elicit more severe and life-threatening side effects when they do occur (Stoner et al., 2002).

Both Haloperidol and Clozapine have been indicated in the treatment of aggression. Clozapine use, however, proves more delicate and complex. It was originally developed in the 1960s but removed from the Canadian market as a result of its serious side effects in 1975. It was released again in Canada in 1991 (Government of Canada, 2018). While Clozapine elicits less extrapyramidal side effects compared to Haloperidol, Clozapine also has an FDA issued black box warning due to possibly serious side effects, including agranulocytosis, a potentially life-threatening complication (Citrome & Volavka, 2013).

The seriousness of the side effects has elicited the requirement of frequent monitoring of blood work and vigilant assessment of residents taking Clozapine, particularly when associated to any febrile illness. In fact, patients on Clozapine must have their blood work sent to the manufacturer, Novartis, for continued assessment. Failure of a patient or physician to submit blood work could induce refusal of the manufacturer to provide the patient with

Clozapine. Since 2003 there have been generic alternatives to Clozapine, which has added complexity to the monitoring process, otherwise simplified in the context of a single manufacturer (Government of Canada, 2018). The severity of side effects of Clozaril and the complex monitoring requirements has caused a great deal of anxiety among practitioners and has lead Clozapine to be a "last resort therapy" despite the promising research findings. However, Clozapine has not been found to be of any clinical utility in treating negative symptoms of schizophrenia (Rosenheck et al, 1999). Notably, negative symptoms of schizophrenia are not usually associated with aggression and violence (Ko et al., 2007).

Resulting from its superior efficacy in treating complicated, positive schizophrenia symptoms, including violence and aggression, Clozapine may be better situated to prevent aggressive incidents among Forensic Patients with a hist ory of aggression.

Method and design

While the clinical question is specific in nature, in order to gain a full and complete understanding of the evidence, it is important to review multiple different sources of reference. It is also important to understand that not all research is of equal methodological rigour and therefore all available evidence specific to the topic should be selected, reviewed and analyzed for significance (Hoffmann et al, 2013).

The best research paradigm to answer the clinical question would be that of a systematic review of the literature and a quantitative analysis of the evidence. Particular attention is being given to studies based on a randomized controlled trial (RCT) method, considered most appropriate in answering the research question. Alternative research methods may be of use, such as observational studies including cohort and case control studies. In fact, research has shown that observational studies can provide as much accuracy as RCTs in delineating effectiveness of interventions. However, while in the process of making clinical decisions, Hoffmann et al. (2013) suggest following the clinical evidence hierarchy in which RCTs are the gold standard for consideration in practice decisions.

In searching to answer the posed clinical question, a group of key terms were used and combined with Boolean operators to ensure that research articles were specific enough to the question and to aid in the elimination of irrelevant research. Truncation was also used where appropriate. The key concepts of the research question are Clozapine and Haldol, violence and/or aggression. Forensic psychiatry, while indeed framing the context and being significant to the question being proposed, does not exclude similar research done outside of a forensic setting. As a result, the key term forensic was included in the key terms; however, it was also left out of some searches as to

ensure that all research investigating violence and aggression and its relationship to Clozapine and Haloperidol use were reviewed. No year limit was placed on the search criteria, permitting the retrieval of any research that may exist on this topic.

The databases used in the search included: Medline, PubMed, ProQuest Nursing and Allied Health and PsychINFO. The following are the key terms used along with the hits they produced:

Clozapine AND Haloperidol AND aggression OR violence AND forensic patients = 141

Clozapine AND aggression AND violence = 20

Clozapine AND haloperidol AND aggression = 19

Clozapine AND haloperidol AND aggression AND forensic = 2

In searching for evidence, emphasis was placed on studies using RCT and/or observational methods. The abstracts of articles matching the key terms of Clozapine or Clozaril and Haloperidol or Haldol were briefly reviewed. If the abstract indicated that the study was in fact a primary study, investigating in some capacity, the effects of Haloperidol and Clozapine and its relation to violence and/or aggression, the study was reviewed for consideration in answering the clinical question. The language was restricted to English for simplicity.

A set of inclusion and exclusion criteria were used to determine which studies to review and select. The following were the inclusion criteria, or the criteria that was necessary for the article to be selected: being a primary research study; investigate, in some capacity, violence and/or aggression in forensic psychiatric or general psychiatric patients with a history of aggression; Clozapine usage and Haloperidol usage. The only exclusion criteria applied was that of research investigating aggression in pediatric psychiatry, as forensic treatment units generally treat adult patients.

In total, 5 primary research studies were found to be specific to the clinical question and its context. One of the studies used a randomized, double blinded design over 6 months (Volavka et al., 2004), one study was a prospective naturalistic study (Bitter et al., 2005), one was a naturalistic, retrospective database analysis (Stoner et al., 2002), one was a non-randomized six-month study (Spivaket et al., 2003) and another one was a mirror image study, an observational type design (Chengappa et al., 2002). Dates of publications range between 2002-2005. Sample size ranged from 44 to 7,655 for a total of N=8,077 for all studies.

There were multiple other studies investigating different antipsychotic medications, such as Quetapine and Risperidone, in its mitigation of violence and/or aggression. While some of these studies were briefly reviewed, they did not serve to answer the specific question at hand, which is that of the effectiveness of haloperidol vs. clozapine in the prevention of

aggression/violence and thus were considered not relevant in answering the specific clinical question.

Summary of Results

The selected research studies are quite diverse and vary in their primary aim of study. All of them investigated aggression and violence in some capacity and the effect that Haloperidol and/or Clozapine had on violence. One study by Chengappa et al. (2002) investigated Clozapine vs. all other antipsychotic medications that patients were prescribed in a state psychiatric hospital. However, these authors indicated that the non-Clozapine treated group was primarily treated with "first generation neuroleptic agents" (p.4) which would include Haloperidol. These authors also stated that "At the time of the study, other second generation antipsychotic agents such as risperidone, olanzapine or quetiapine were not available" (p.4).

All but one of the authors (Bitter et al., 2005) found that Clozapine treated patients displayed a significant reduction in violent behavior/aggression, compared to Haloperidol treated patients. However, in their prospective, naturalistic study, Bitter et al. (2005) found that Olanzapine and Risperidone were significantly superior to Haloperidol and Clozapine in reducing violence. Interestingly, in the study by Volavka et al. (2004), it was reported that Risperidone and Olanzapine showed better improvement in psychotic symptoms in patients who exhibited less aggressive behaviours. However, in patients with more aggressive behaviour, Clozapine was superior to all antipsychotics including Haloperidol.

The most common diagnosis of participants in the five studies was schizophrenia. Stoner et al. (2002) investigated the effectiveness of Haloperidol and Clozapine in reducing aggressive incidence among forensic patients who had committed violent crimes (including assault, armed criminal actions and burglary) and found that patients using haloperidol were more likely to have their conditional release revoked, in part, due to aggressive and violent behaviour, whereas those treated with Clozapine were less likely to have their conditional release revoked and showed better participation in outpatient programs. Only two studies were forensic specific (Chengappa et al., 2002; Stoner et al., 2002), the rest included outpatients with schizophrenia and a history of violence.

Merit of Evidence and Implications for Practice

Of the 182 studies found to contain the above mentioned key terms, 5 met the inclusion criteria. While the retained research may guide clinical decision making, it also highlights the need for more, high quality research on the true effects of different antipsychotics and their prevention of aggression in forensic psychiatry.

As indicated previously, only two studies were specific to forensic psychiatry (Chengappa et al., 2002; Stoner et al., 2002). The remainder looked at outpatients with a history of violent behaviour. While plenty of research exists on the incidence, prevalence and causes of violence in forensic psychiatry, more is currently needed to review the potential implications of pharmacotherapy as prevention for aggression and violence within a forensic psychiatric context.

However, specifically to the research question, the evidence does show that Clozapine appears to have a better effect than Haloperidol in the prevention of violence and aggression among psychiatric populations with a history of aggression. Receiving Clozapine also appears to reduce violent behavior in forensic psychiatric settings, therefore reducing the need to use both seclusion and restraint (Chengappa et al., 2002). The challenge of Clozapine administration remains the monitoring of side effects and the requirement of adequate, therapeutic dosing before the real effects of Clozapine are seen (Volavka et al., 2004).

Conclusion

While the retained and reviewed research does answer the clinical question, the process of reviewing the literature lead to the development of further clinical questions and highlighted the need for further, forensic specific research. Perhaps, comparisons including other psychotropic formulas could lead to novel strategies of administration of antipsychotics, or a combination of therapeutic methods may prove more efficient in controlling violent outbursts. For this paper, a total of five primary research studies of 182 articles were selected for review. Key terms, as well as inclusion and exclusion criteria were developed and followed in order to ensure the found research was specific and relevant to the topic under investigation. Answering the clinical question has also led to reflection and application of new recommendations of pharmaceutical interventions in a forensic setting.

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